A New era of GDMT: Are we witnessing a convergence of GDMT for heart failure and CKD?

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DISCLOSURES

- Consultancy: AstraZeneca, Alexion, Bayer, Boehringer & Ingelheim, Cambridge Healthcare Research, Novo Nordisk, Travere Therapeutics, Dedham Group
- Speaker honoraria: AstraZeneca, Boehringer & Ingelheim, Cornerstone Medical Education, The Limbic, Medscape, American Diabetes Association, Renal Society of Australasia
- Trial/consortium steering committees: SMART-C, AstraZeneca, Bayer, CSL Behring
- Grants: National Health and Medical Research Council, Medical Research Future Fund, Ramaciotti Foundation (all Australian)

All honoraria paid to my institution

ARE WE WITNESSING A CONVERGENCE OF GDMT FOR HEART FAILURE AND CKD?

Yes and no…

KEY ELEMENTS OF GDMT ARE SHARED ACROSS HEART FAILURE AND CKD

T2D & CKD

"Quadruple Therapy"

- **ACEi/ARB**
- **SGLT2 inhibitor**
- ***Non-steroidal* MRA**
- **GLP-1RA**

HFrEF & HFmrEF

"Quadruple Therapy"

- **ACEi/ARB/ARNI**
- **β-blocker**
- ***Steroidal* MRA**
- **SGLT2 inhibitor**

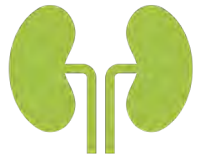
GDMT FOR ONE CONDITION CAN DELAY OR PREVENT ONSET OF THE OTHER

Heart Failure

Chronic Kidney Disease

ACEi/ARB, non-steroidal MRAs, and SGLT2i prevent HF events in CKD

ARNI and SGLT2i slow kidney disease progression in HF

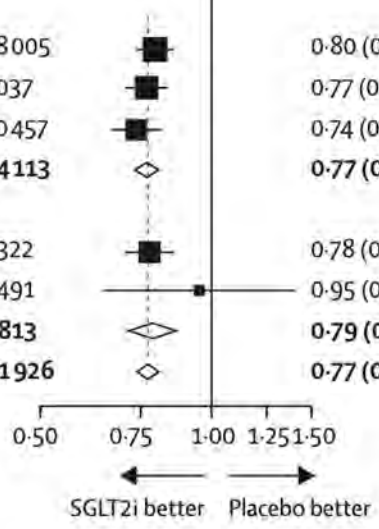


SGLT2I AND NS-MRA REDUCE HF IN CKD

SMART-C

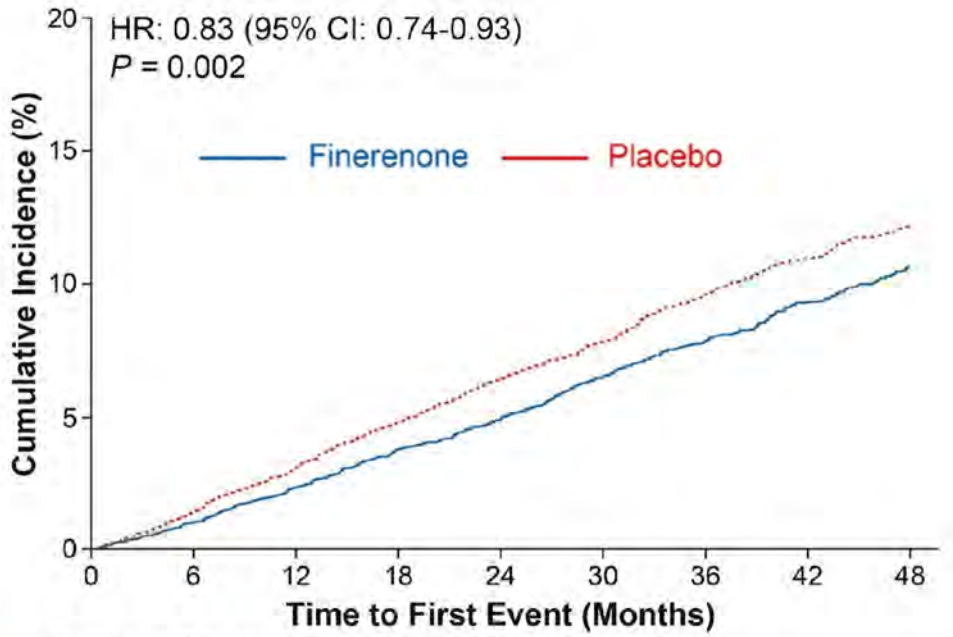
Cardiovascular death or hospitalisation for heart failure*

	Mean baseline eGFR, mL/min per 1·73m²	Events/participants SGLT2i	Events/participants Placebo	RR (95% CI)
Diabetes				
High atherosclerotic cardiovascular risk trials	80	1490/24563	1232/18005	0·80 (0·74–0·86)
Stable heart failure trials†	61	923/5046	1154/5037	0·77 (0·71–0·84)
Chronic kidney disease trials	45	643/10474	847/10457	0·74 (0·66–0·82)
Subtotal: diabetes	**67**	**3056/40691**	**3233/34113**	**0·77 (0·73–0·81)**
No diabetes				
Stable heart failure trials†	64	710/5316	890/5322	0·78 (0·70–0·86)
Chronic kidney disease trials	40	50/2476	53/2491	0·95 (0·65–1·40)
Subtotal: no diabetes	**56**	**760/7792**	**943/7813**	**0·79 (0·72–0·87)**
Total: overall	**65**	**3816/48483**	**4176/41926**	**0·77 (0·74–0·81)**



NDPH Renal Studies Group & SMART-C The Lancet 2022

FIDELITY

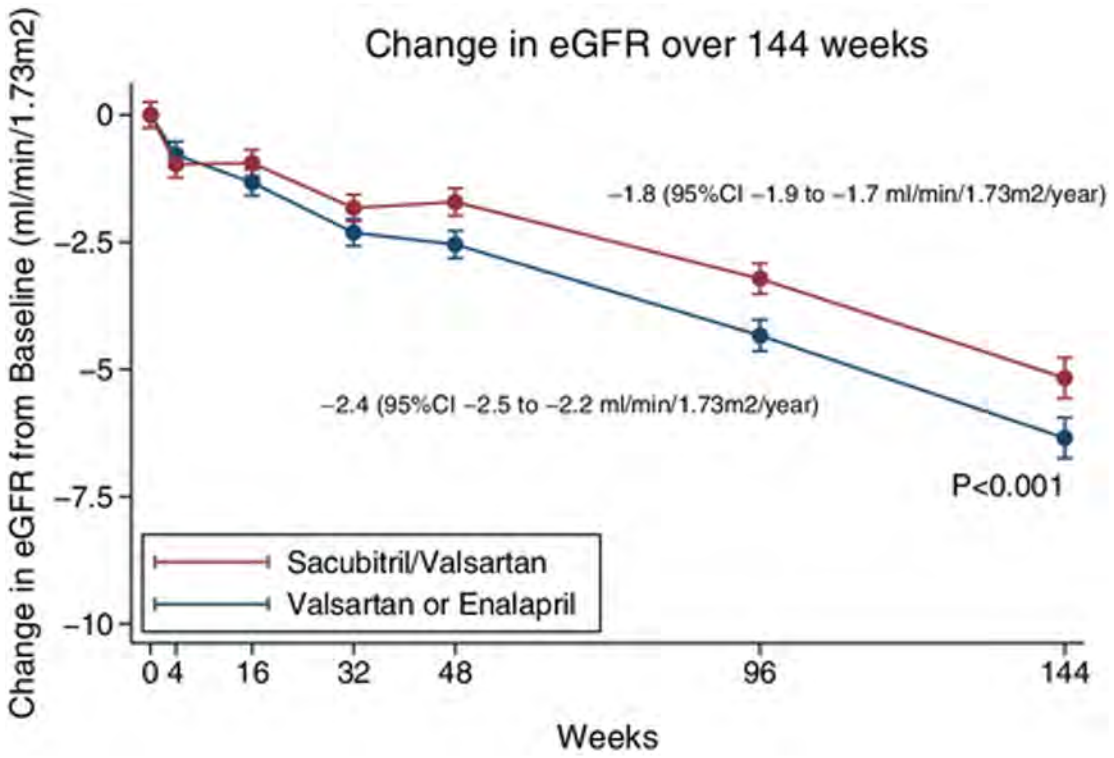


Number of Patients at Risk

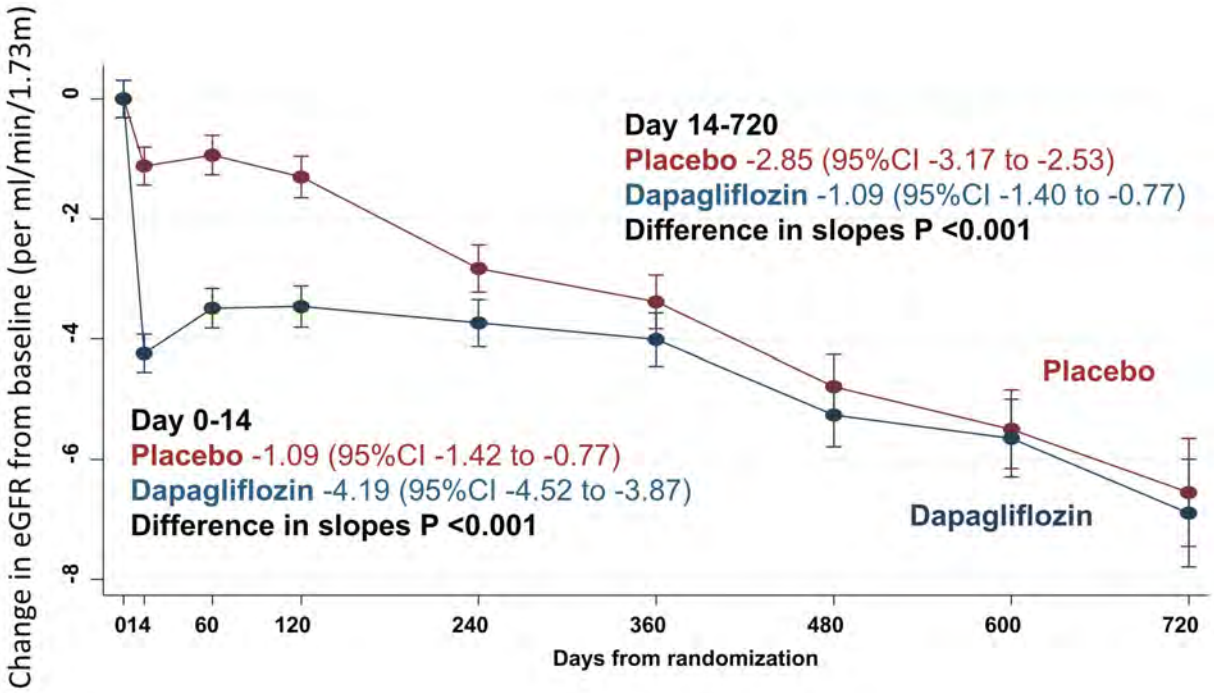
Finerenone	6,519	6,431	6,313	6,167	5,449	4,379	3,202	2,299	1,143
Placebo	6,507	6,394	6,246	6,102	5,379	4,342	3,138	2,271	1,144

Filippatos G et al. JACC HF 2022

ARNI & SGLT2I ATTENUATE GFR DECLINE IN HF



PARADIGM-HF & PARAGON-HF
McCausland FR et al. Eur J Heart Fail 2022



DAPA-HF
Jhund P et al. Circulation 2021

NEWER COMPONENTS OF GDMT CAN ENHANCE THE TOLERABILITY OF RAS BLOCKADE AND MRA

Heart Failure

SGLT2i may enable persistent MRA use in HF

ARNI may enable persistent MRA use in HF

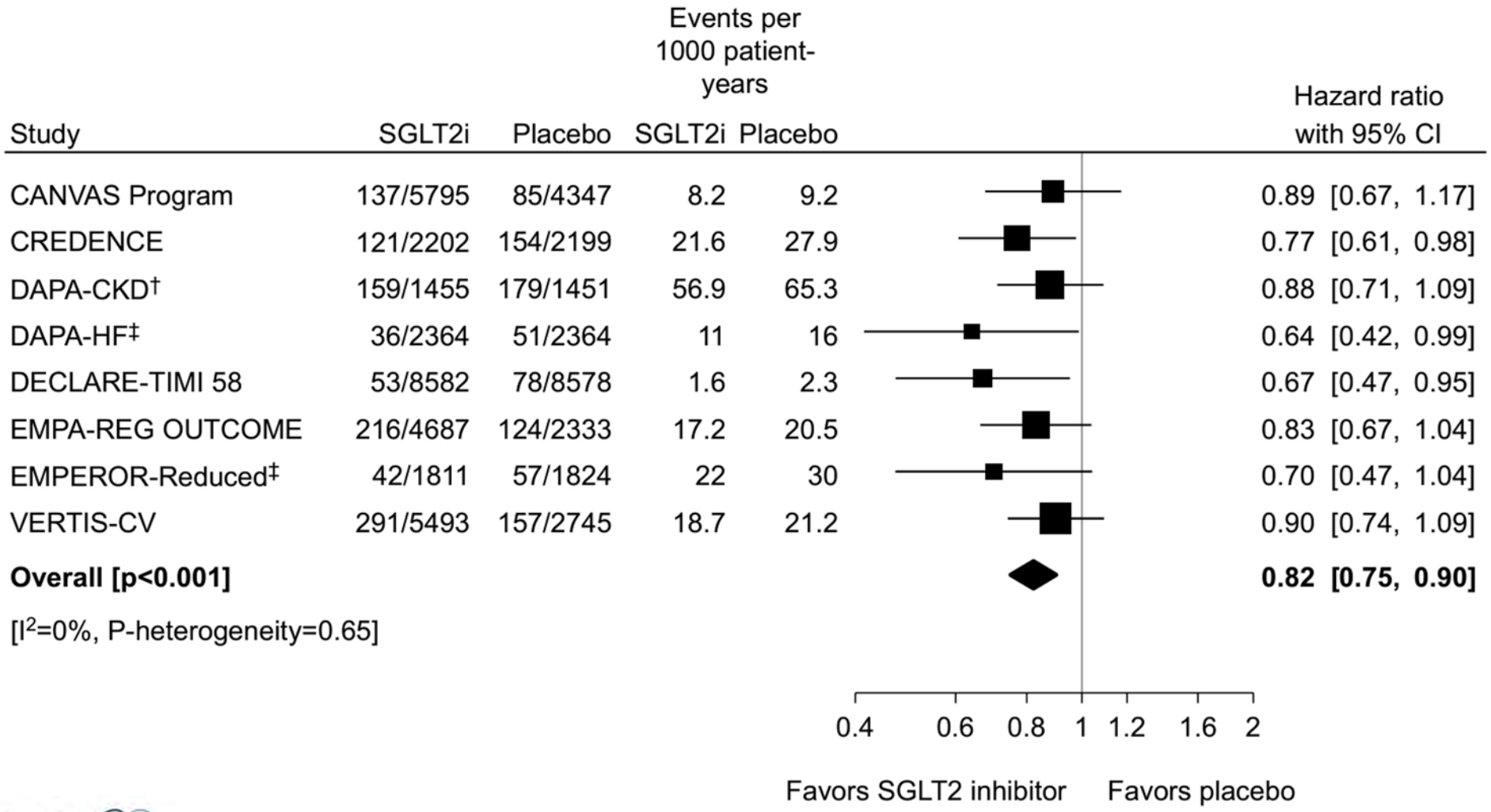
Chronic Kidney Disease

SGLT2i enables persistent use of RASi in CKD

SGLT2i may enable persistent use of ns-MRA in CKD

SGLT2i may facilitate safer use of ETA-RA in CKD

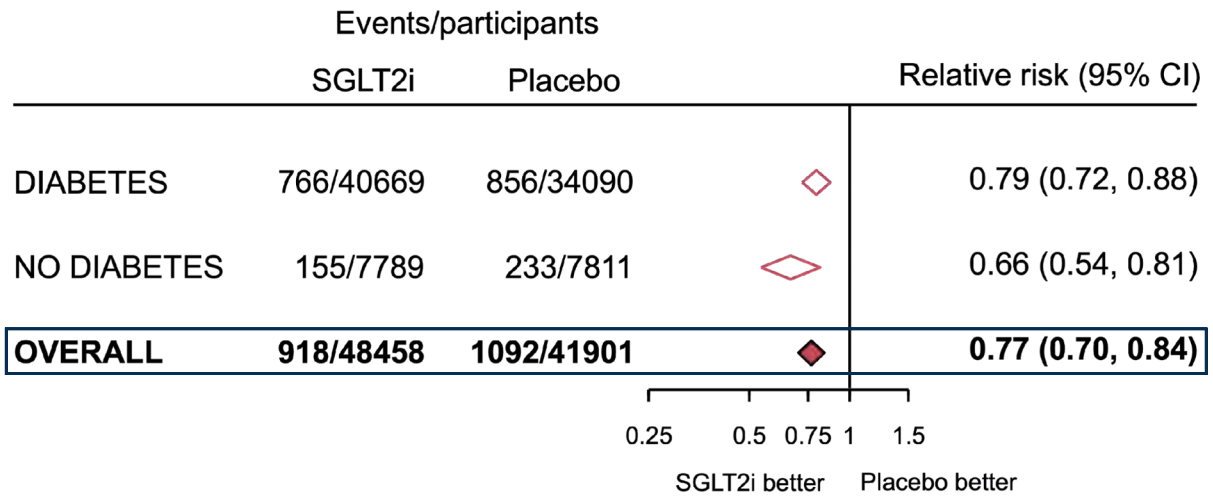
SGLT2i REDUCES HYPERKALEMIA (K>6.0 MMOL/L)



Neuen BL et al. Circulation 2022

SGLT2i reduces AKI and Hospitalisations

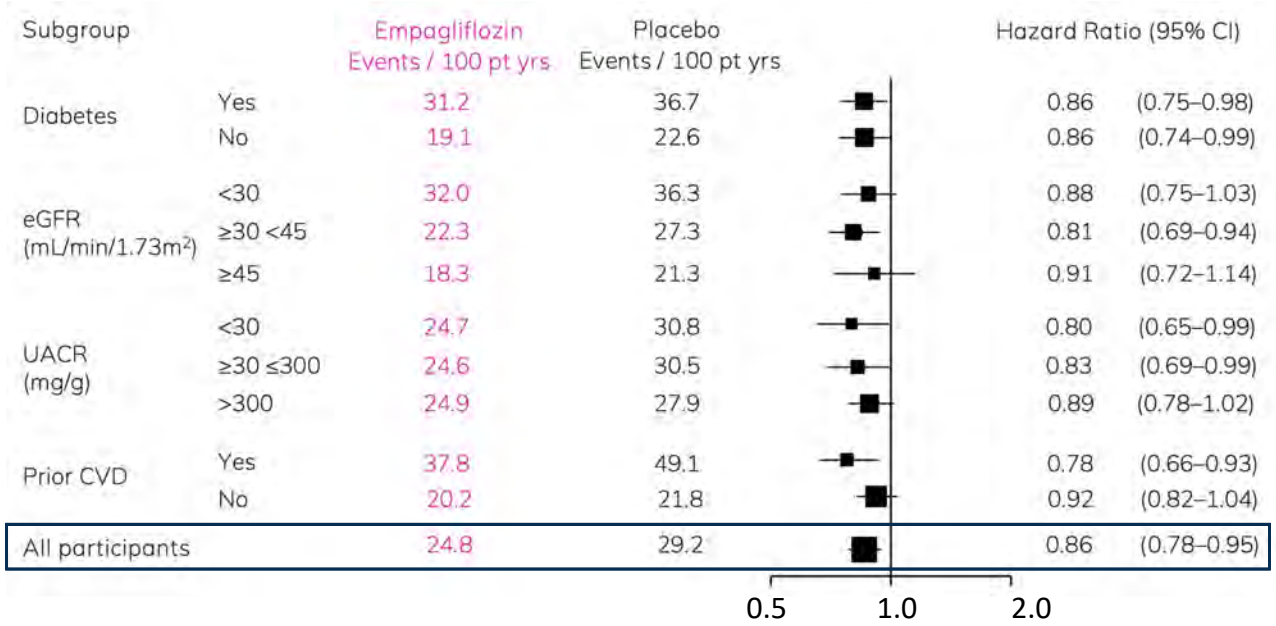
Acute kidney injury



Heterogeneity by diabetes status: p=0.12

NDPH Renal Studies Group & SMART-C The Lancet 2022

EMPA-KIDNEY: All-cause hospitalization



Preiss D et al. AHA 2022

Effect of SGLT2 inhibitors on discontinuation of RAS blockade: A joint analysis of the CREDENCE and DAPA-CKD trials

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

METHODS

Two randomized, double-blind, placebo-controlled trials

8483 participants

Temporary (≥4 weeks) or permanent discontinuation of ACEi or ARB

OUTCOME

SGLT2 inhibitor

4.0
per 100 patient years

HR 0.85
95% CI 0.74-0.99

Placebo

4.7
per 100 patient years

Consistent effect across:

- GFR
- RAS blockade dose
- Serum K+

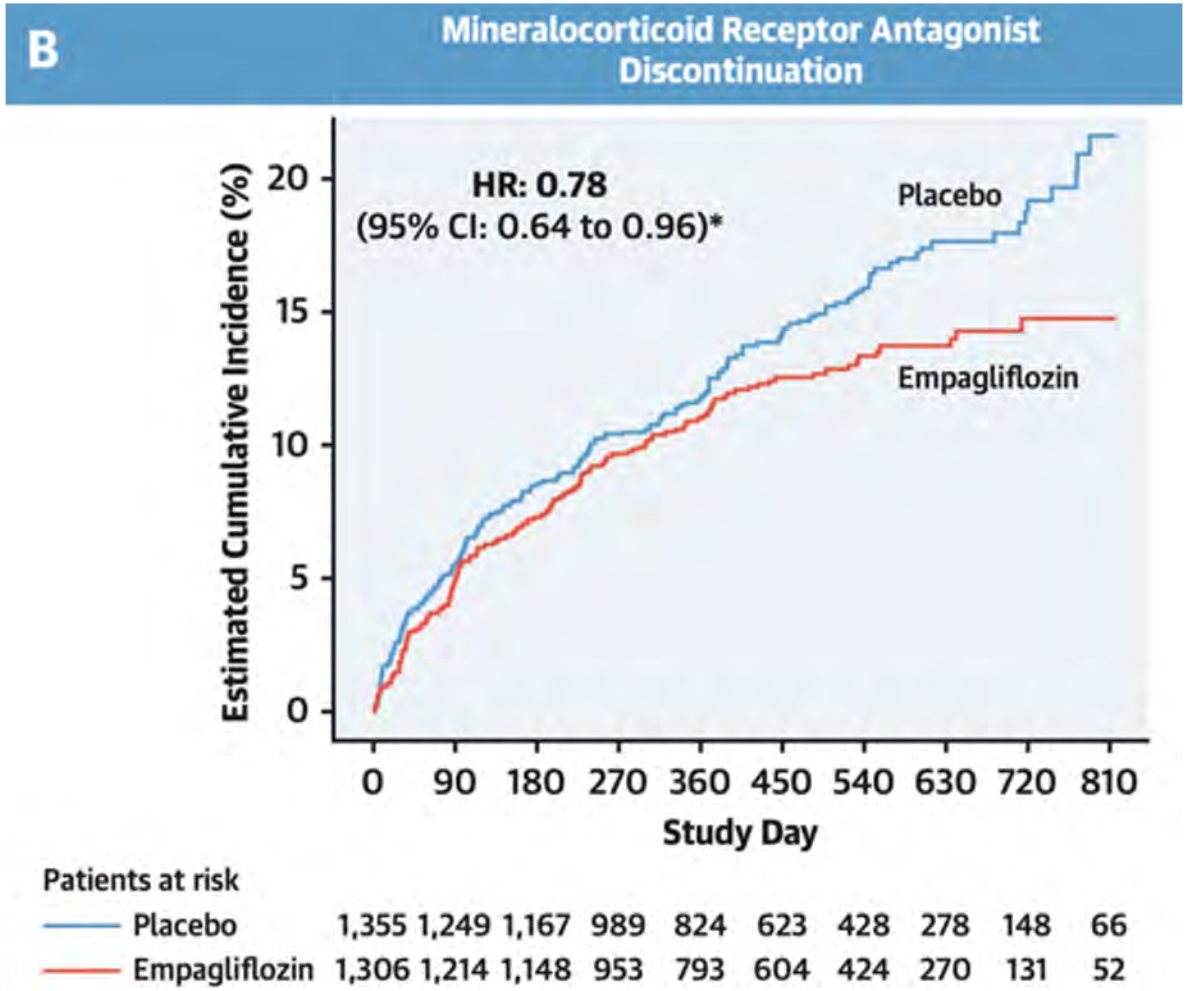
More pronounced effect:

- UACR ≥1000 mg/g
  P-interaction=0.01

Conclusion
In patients with albuminuric CKD, SGLT2 inhibitors facilitate persistent use of RAS blockade.

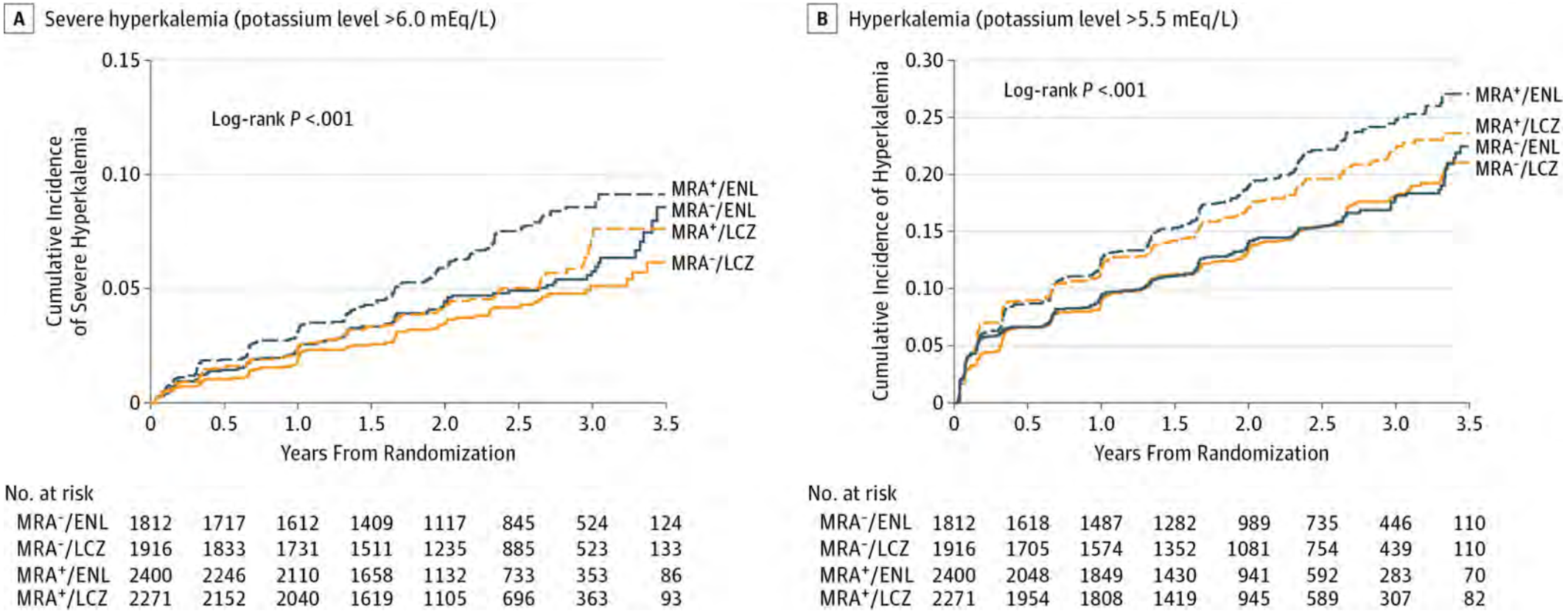
Fletcher RA… Neuen BL
J Am Soc Nephrol 2023
doi:10.1681/ASN.0000000000000248

SGLT2I REDUCES MRA DISCONTINUATION IN HFREF



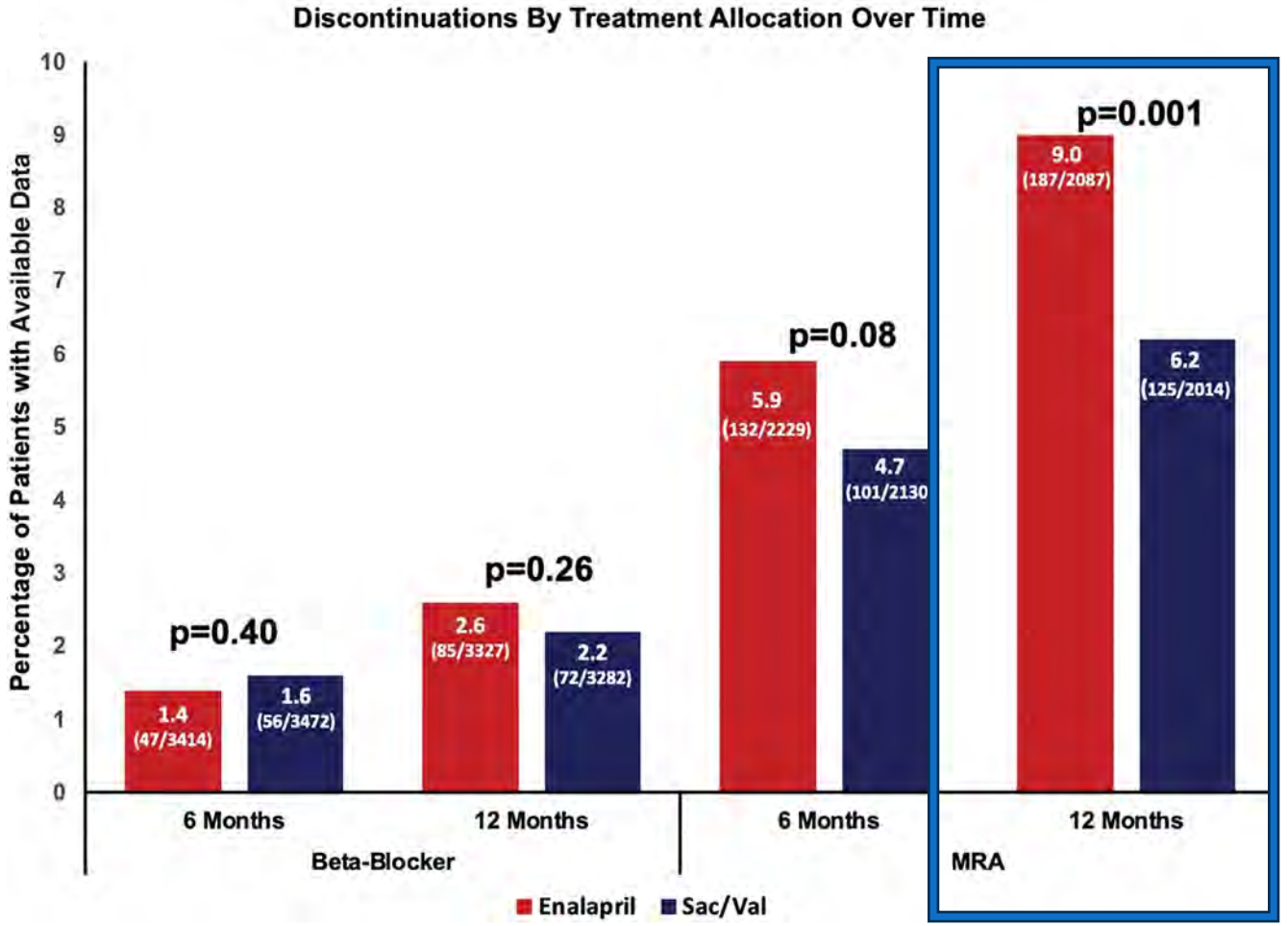
Ferreira et al. JACC 2022

INCIDENCE OF HYPERKALEMIA LOWER WITH ARNI VS. ACEI IN HFREF



Desai AS et al. JACC HF 2022

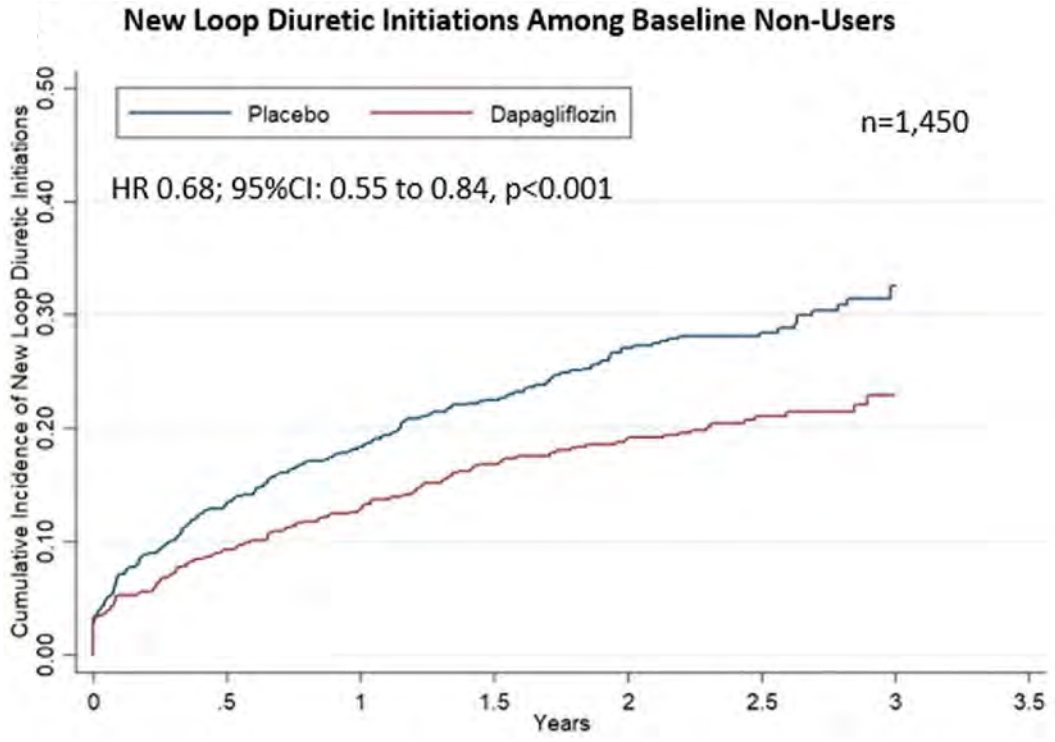
ARNI REDUCES MRA DISCONTINUATION IN HFrEF



Bhatt AS et al. Eur J Heart Fail 2022

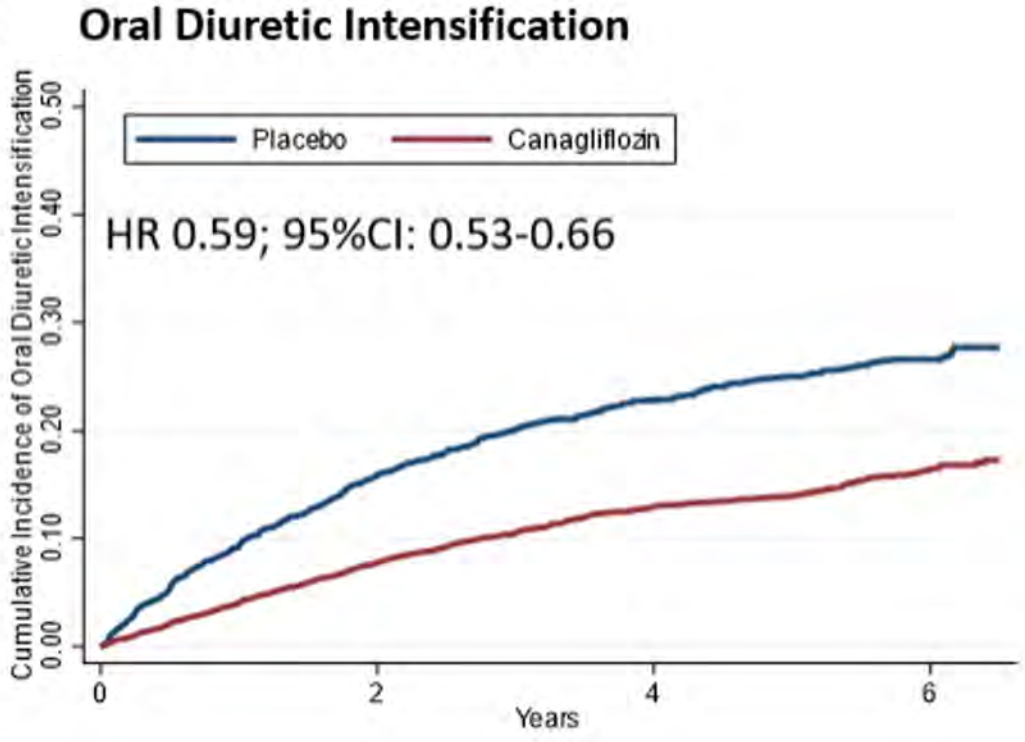
SGLT2I REDUCES DIURETIC INITIATION/INTENSIFICATION IN CKD & HF

DELIVER



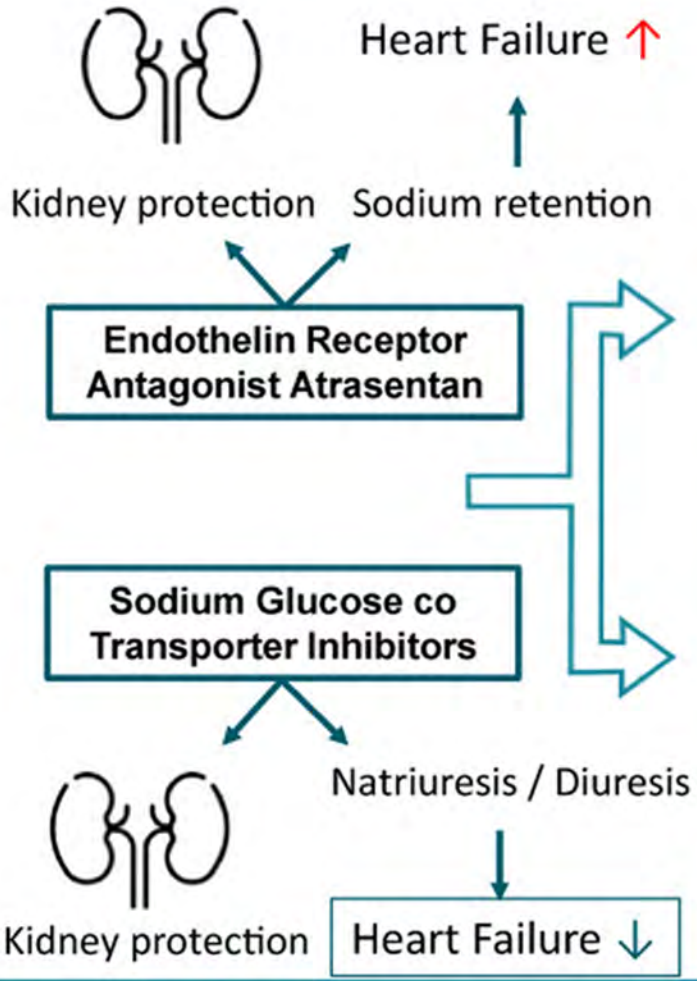
Chatur S et al. Circulation 2023

CANVAS/CREDENCE



Chatur S… Neuen BL (unpublished)

New insights from SONAR indicate adding sodium glucose co-transporter 2 inhibitors to an endothelin receptor antagonist mitigates fluid retention and enhances albuminuria reduction.

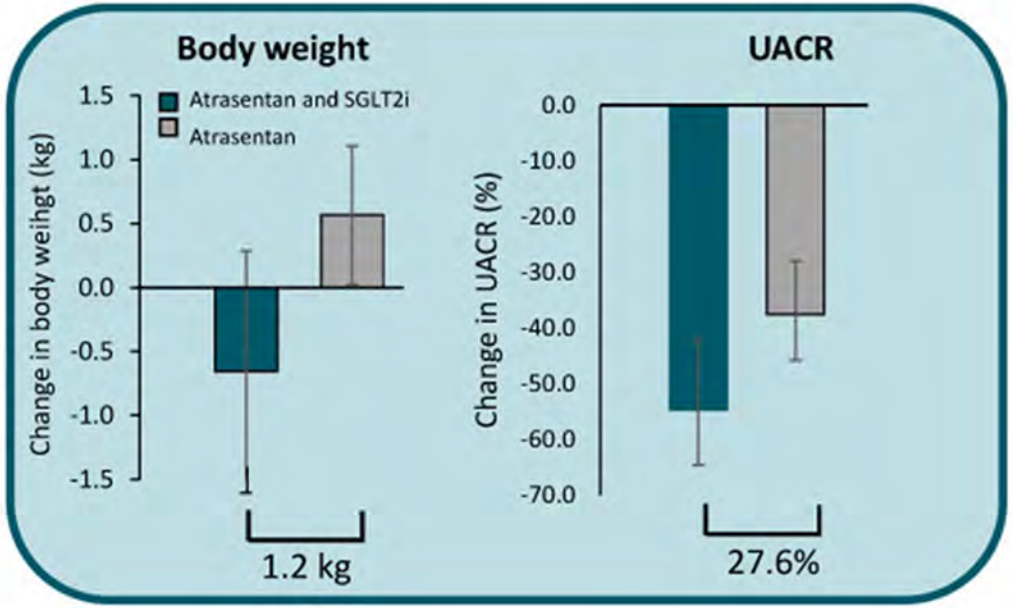


Selection and matching

Matched Case Control

	Atrasentan and SGLT2i (N=14)	Atrasentan (N=42)
Age, years	66	65
Female sex, n/%	4 (28.6)	13 (31.0)
Body weight, kg	102	102)
Systolic BP, mmHg	142	143
eGFR, ml/min/1.73m^2	42	41
UACR, mg/g	465	632
BNP, pg/ml	52	51
Diuretics, n/%	13 (92.9)	38 (90.5)

Results



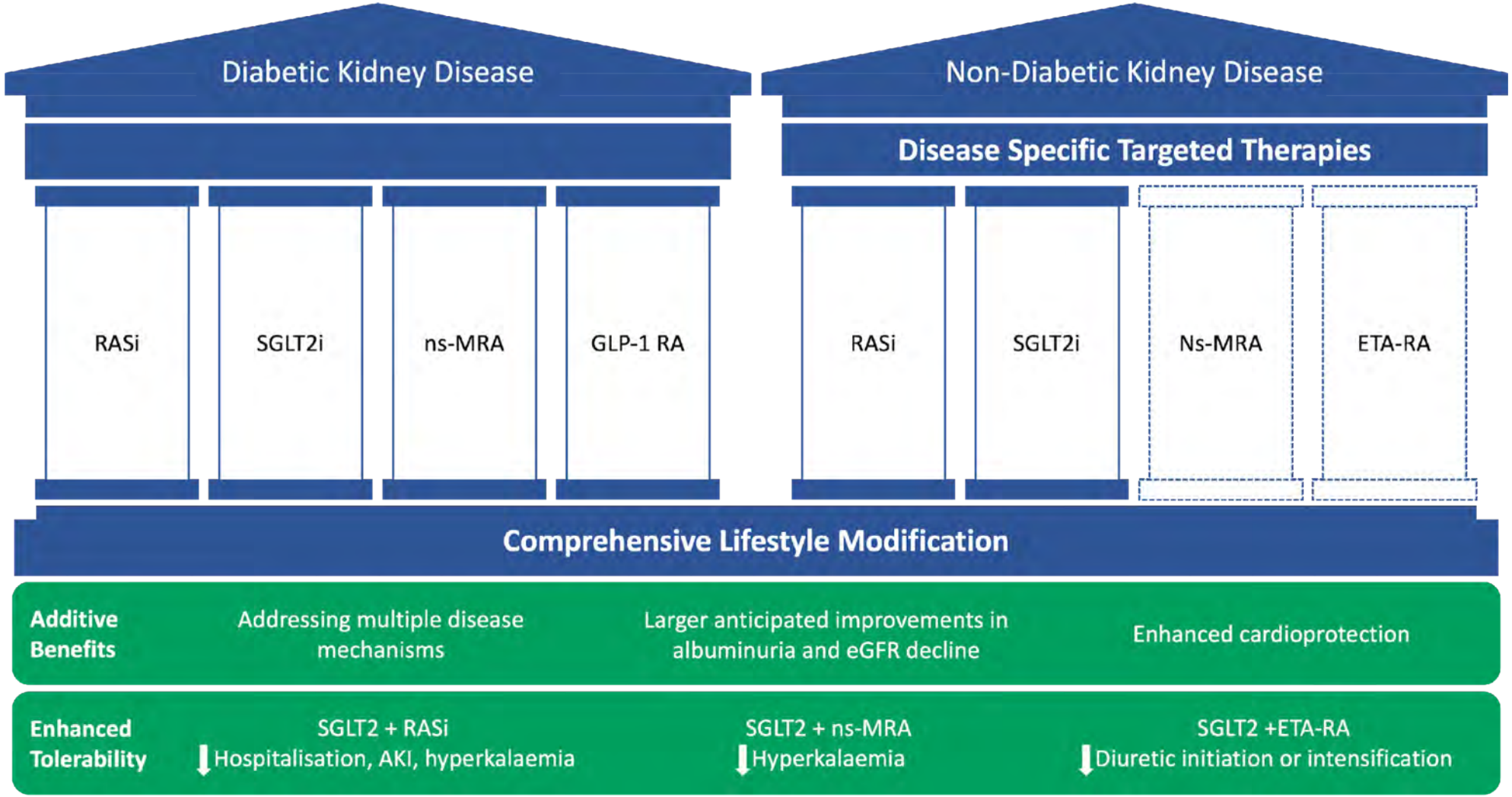
CONCLUSION:

Six-weeks combined SGLT2i/atrasentan treatment versus atrasentan alone decreased albuminuria and body weight supporting future studies to characterize the long-term efficacy and safety of combined SGLT2i/ERA treatment.

ISN kidney INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

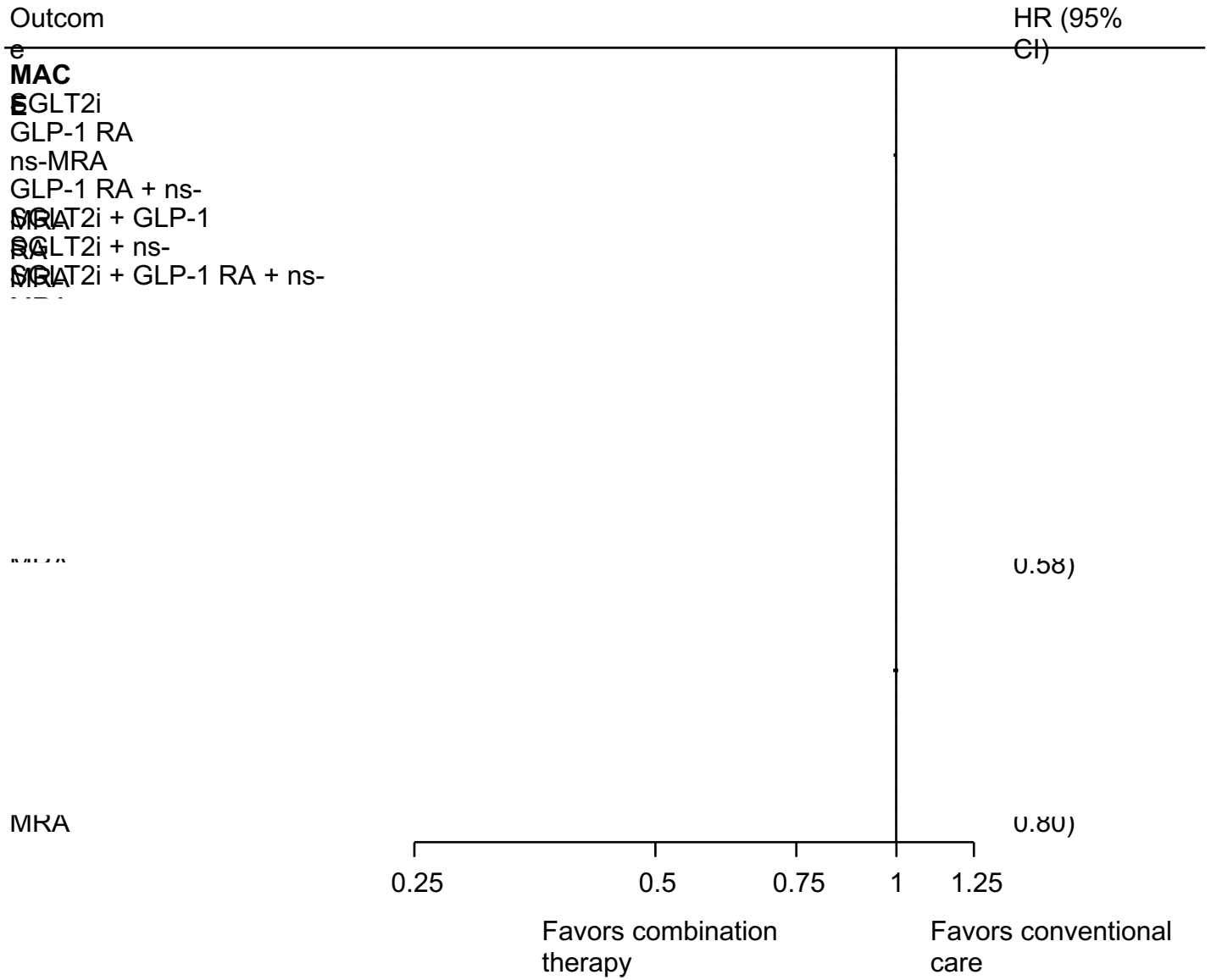
Heerspink H.J.L. et al, 2020

CONTEMPORARY KIDNEY GDMT IN 2024



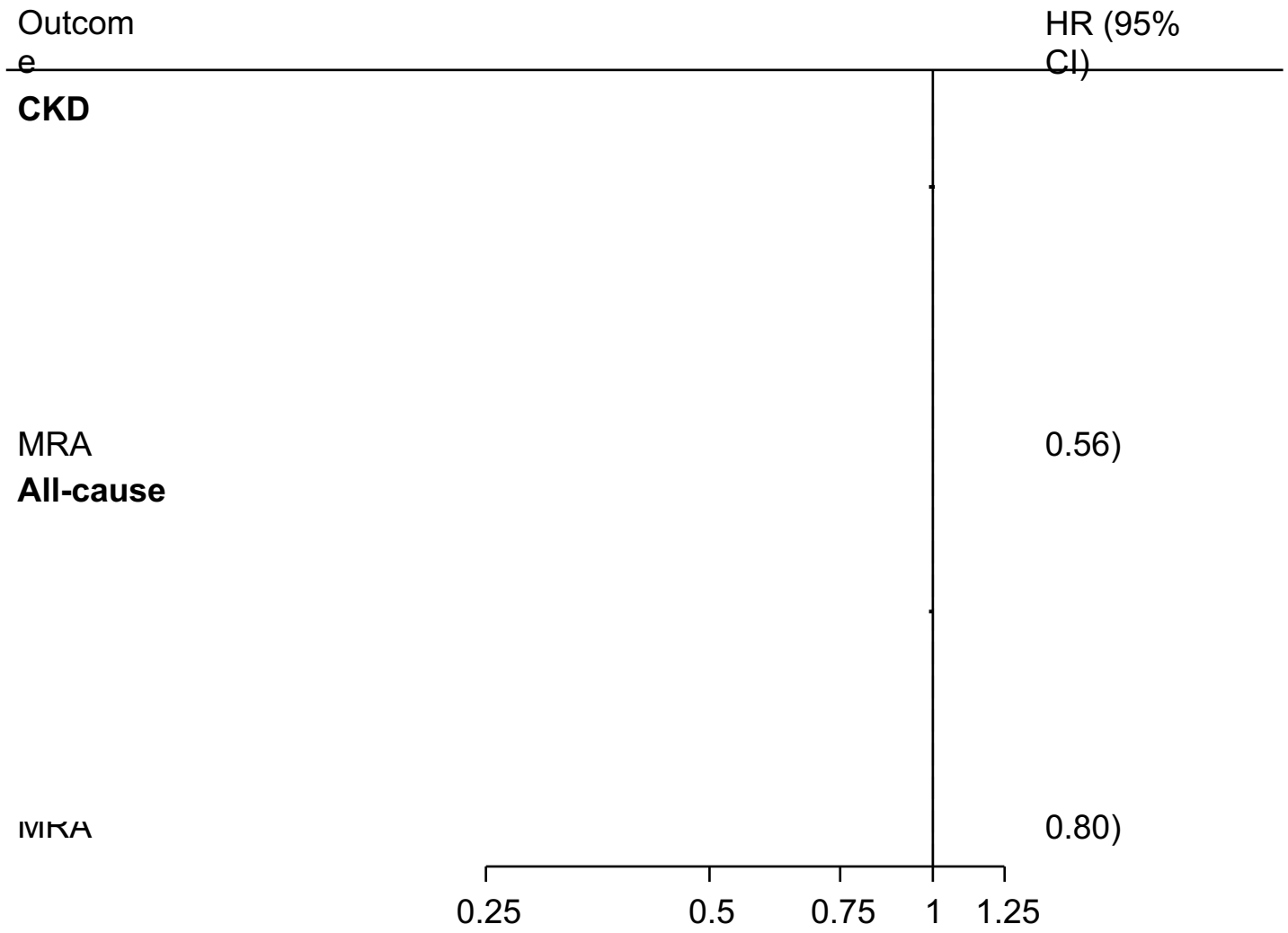
Neuen BL et al. (under review)

4 PILLARS OF GDMT IN DIABETES & CKD



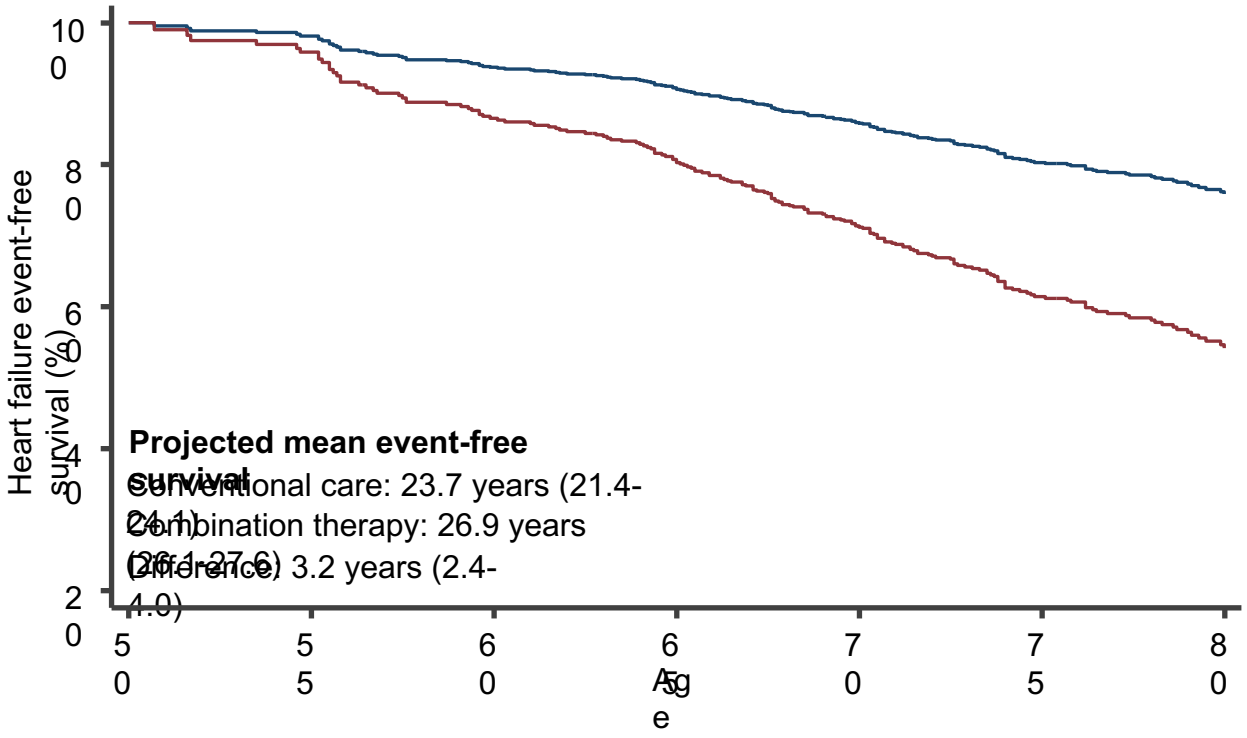
Neuen BL et al. Circulation 2024

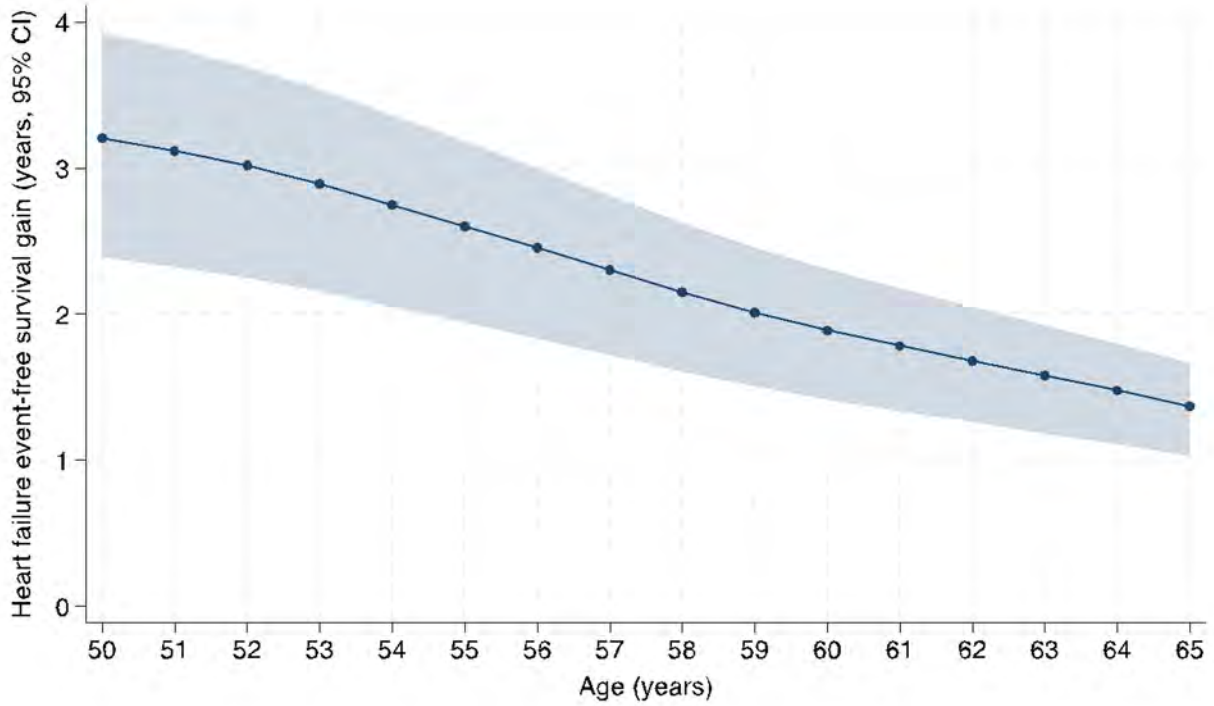
4 PILLARS OF GDMT IN DIABETES & CKD



Neuen BL et al. Circulation 2024

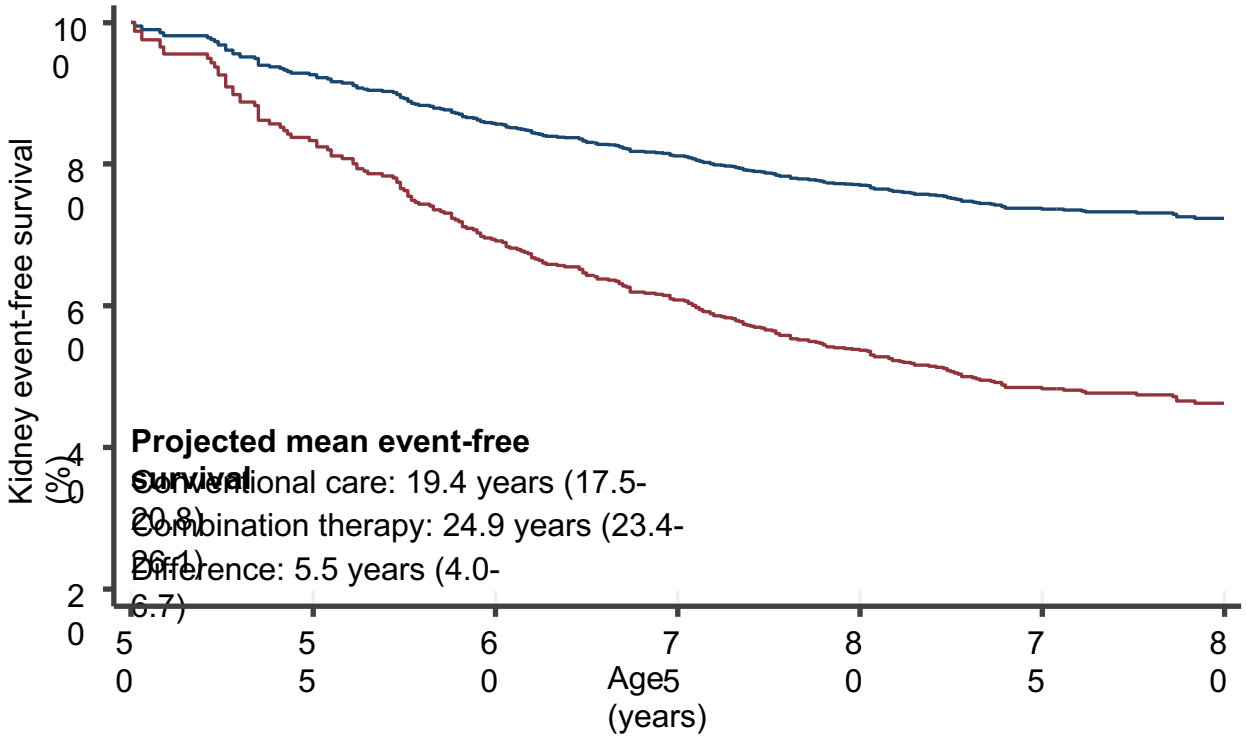
HEART FAILURE EVENT-FREE SURVIVAL WITH COMBINATION GDMT IN DIABETES & CKD

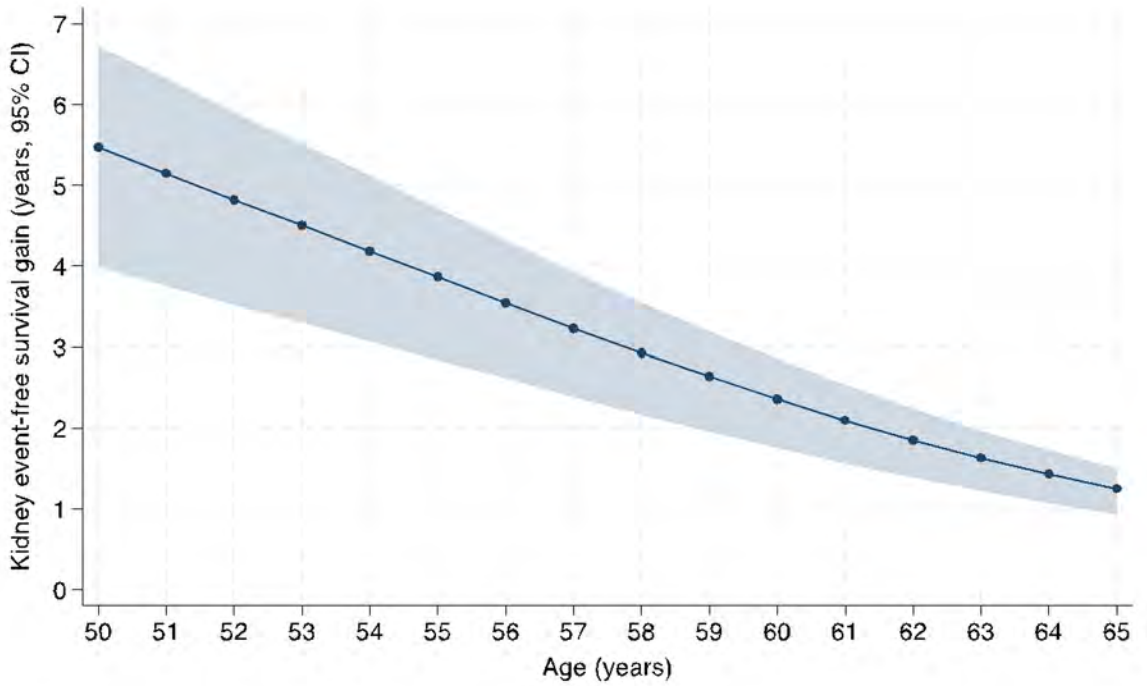




Neuen BL et al. Circulation 2024

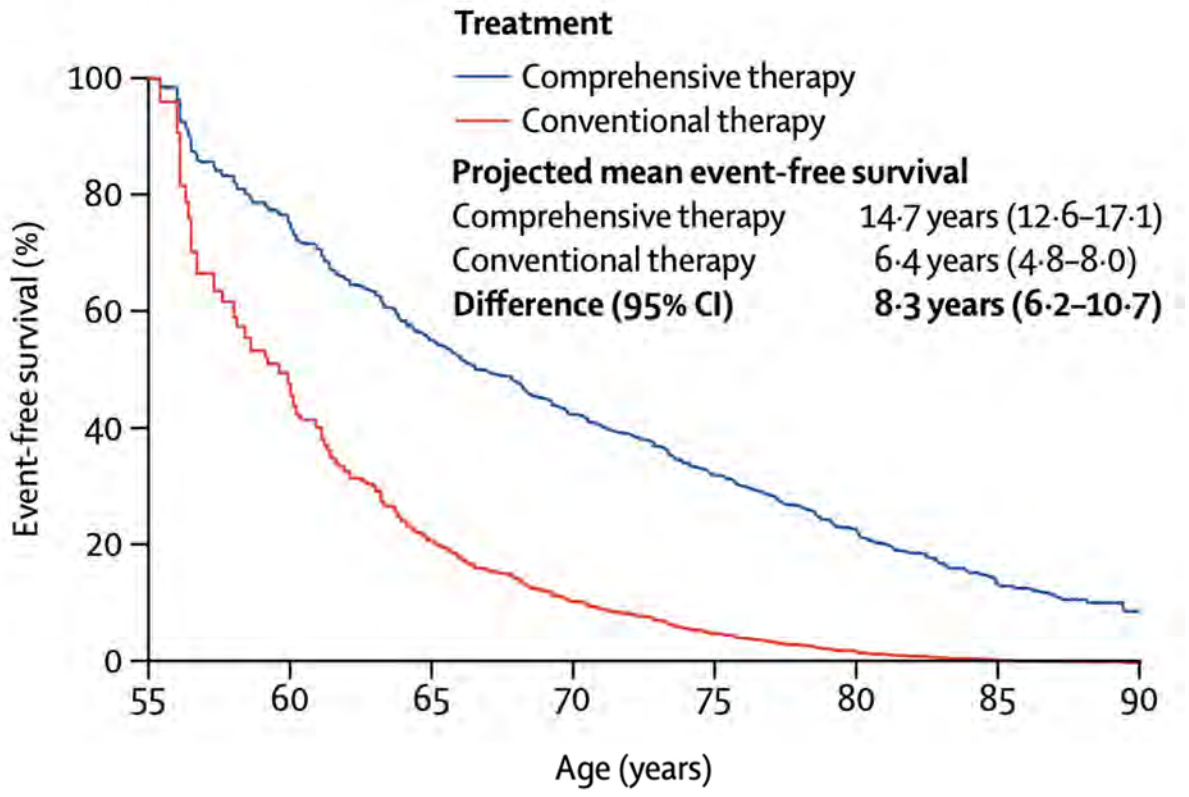
HEART FAILURE EVENT-FREE SURVIVAL WITH COMBINATION GDMT IN DIABETES & CKD

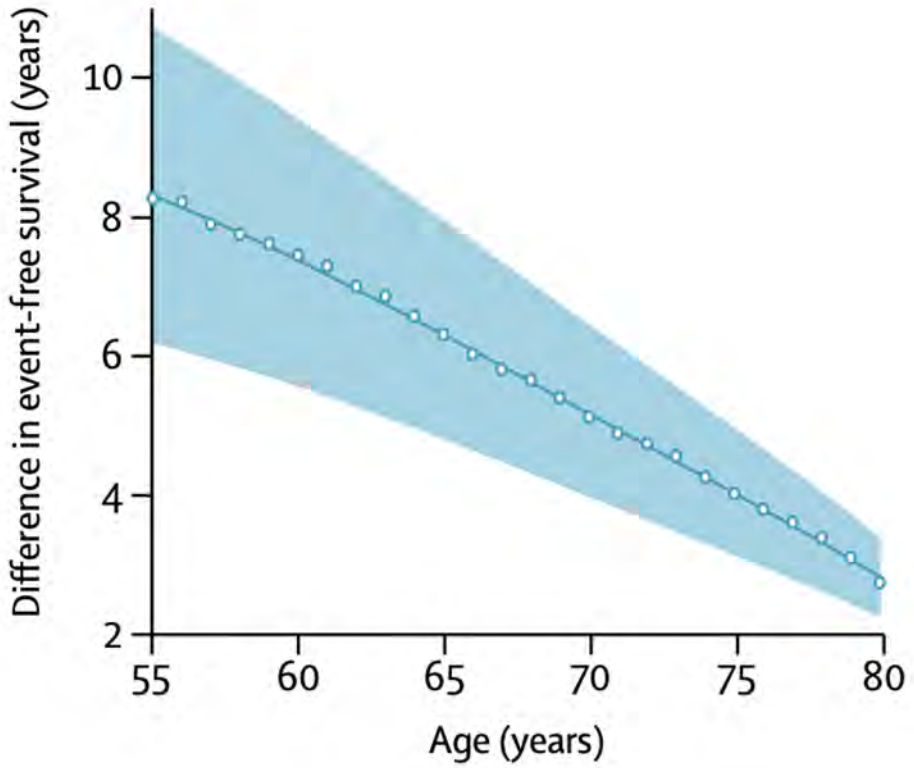




Neuen BL et al. Circulation 2024

HEART FAILURE EVENT-FREE SURVIVAL WITH COMBINATION GDMT IN HFrEF





Vaduganathan M et al. The Lancet 2020

THEORETICAL APPROACHES TO IMPLEMENTING THE "4 PILLARS" IN CKD

TRADITIONAL APPROACH

RAS blockade, add SGLT2i, re-assess in 3-6 months, add ns-MRA, consider GLP-1 RA

Limitations: Ignores excess early cardiovascular risk, very high risk of therapeutic inertia

RAPID SEQUENCE APPROACH

Rapid sequence implementation of "kidney GDMT"

Considerations: Assumes all patients with CKD are at equally high-risk, cost-effectiveness uncertain, and safety largely untested

ACCELERATED RISK-BASED APPROACH

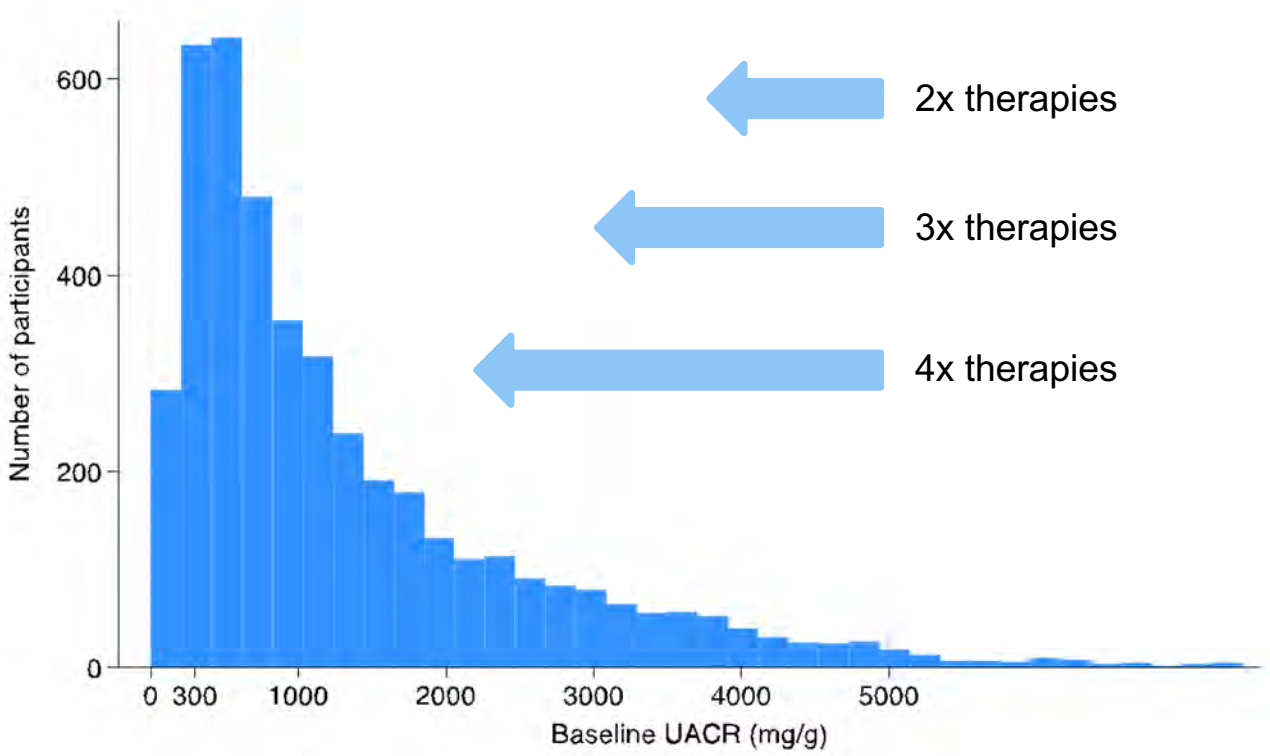
Identify patients at highest risk using validated risk score, prioritise accelerated implementation of combination guideline directed medical therapy

Appeal: Match intensity of treatment to risk, prioritise patients likely to obtain greatest absolute benefits

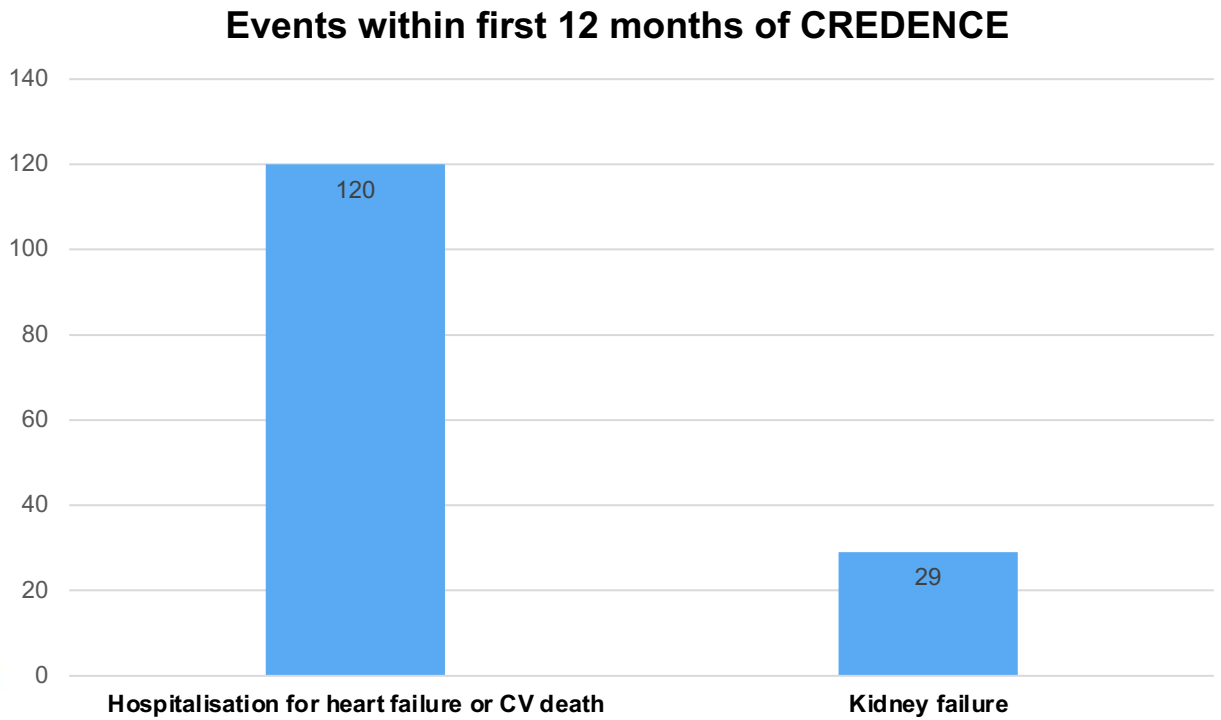
Neuen BL, Tuttle KR & Vaduganathan M. Circulation 2024 (in press)

RATIONALE FOR UP FRONT COMBINATION THERAPY: CREDENCE

Many individuals will need combination therapy



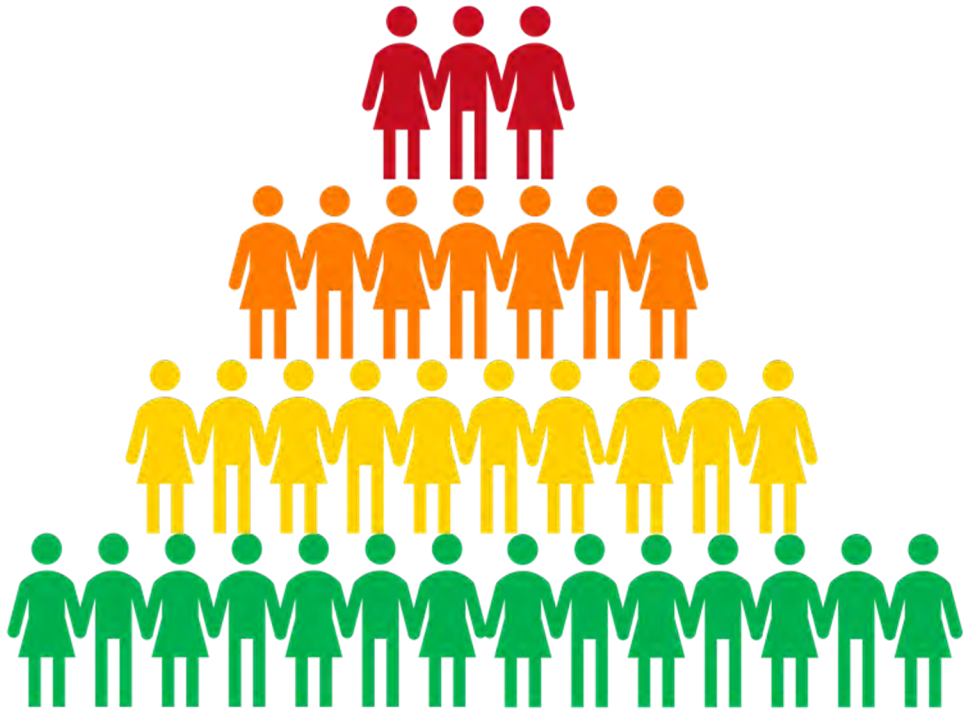
Excess early risk is predominantly due to CVD

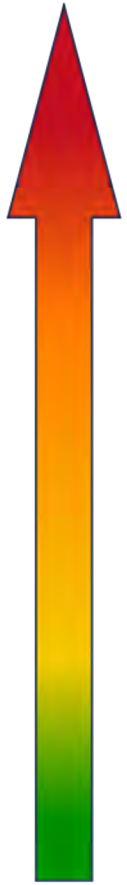


MATCH INTENSITY OF GDMT TO RISK

Accelerated risk-based implementation of guideline directed combination therapy for type 2 diabetes and CKD

Stratify risk using validated risk score
(e.g. KDIGO heat map or KFRE)





<u>Very high/high risk</u>

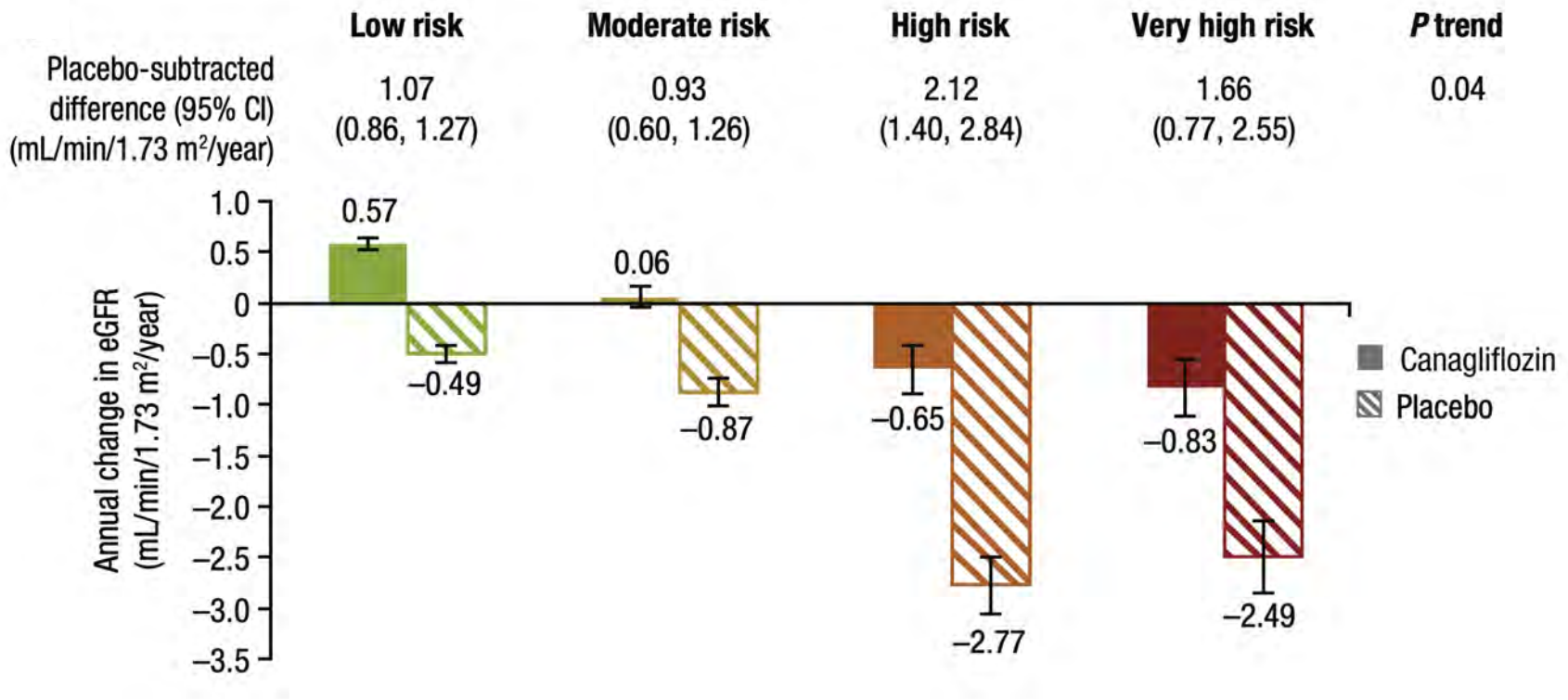
- Early nephrology referral
- Up-front, accelerated sequence combination therapy

<u>Moderate/low risk</u>

- Primary care management
- As needed specialist referral
- Traditional, sequential add-on therapy

Neuen BL, Tuttle KR & Vaduganathan M. Circulation 2024 (in press)

RISK-BASED APPROACH: ACCELERATED IMPLEMENTATION FOR THOSE AT HIGHEST RISK



Concept: Use validated risk score to identify which patients gain greatest absolute benefits → accelerated uptake of kidney GDMT

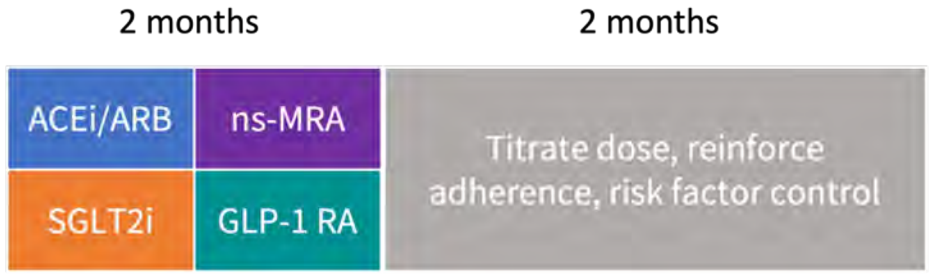
Neuen BL et al. Am J Kidney Dis 2021

TIMING AND SEQUENCING OF KIDNEY GDMT (AND HF)

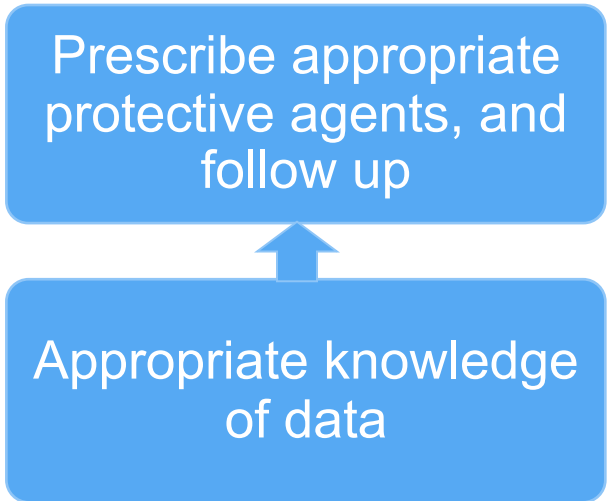
Traditional/conservative approach

Accelerated approach

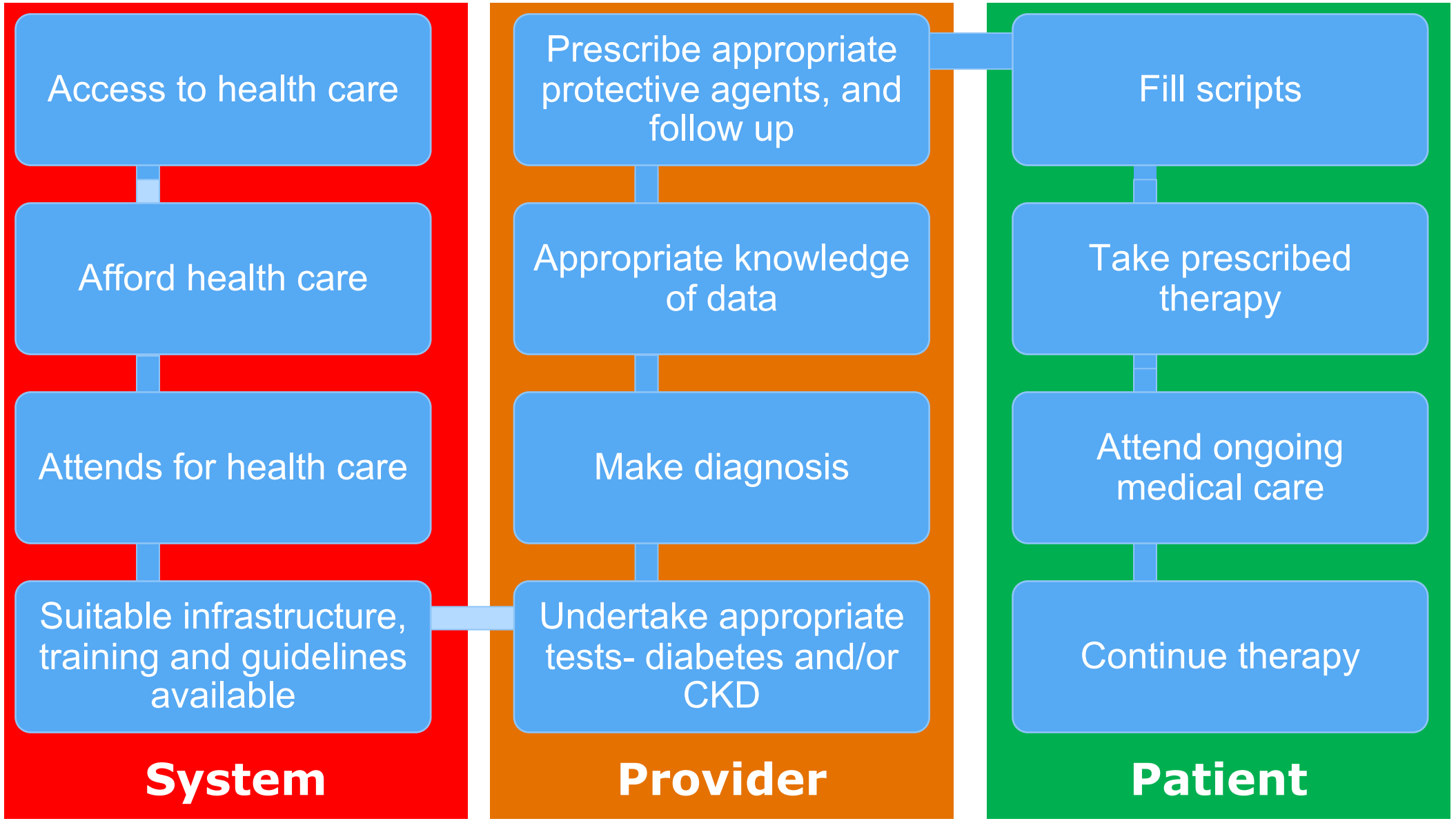
Rapid sequence approach



It can take up over 12 months until guideline directed medical therapy for type 2 diabetes and CKD is fully implemented


Prescribe appropriate protective agents, and follow up
Appropriate knowledge of data

Requirements For Full Utilisation of Proven Therapies



Kim D, Perkovic V, Kotwal S. KI Reports 2024

Are we witnessing a convergence of GDMT for HF and CKD?

Yes:

- Key elements of GDMT are shared across heart failure and CKD
- GDMT for one condition can delay or prevent the onset of the other
- Newer components of GDMT can enable better use of RASi & MRA in both conditions
- Common unanswered questions about timing and sequencing
- Common implementation challenges

No:

- Greater heterogeneity in risk of CKD progression
- Unique treatment considerations in CKD (e.g. negative acute effects on GFR)
- Not all future components of CKD GDMT likely to reduce HF risk (e.g. ETA-RA)
- Need for disease-specific, targeted therapies for non-diabetic CKD (e.g. GNs)